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Treatment of Plasma Refractory Thrombotic Thrombocytopenic Purpura With Protein A Immunoabsorption

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The objective of this study was to assess the effect of protein A immunoabsorption in terms of response rate and toxicities in patients with classical thrombotic thrombocytopenic purpura (TTP) refractory to therapeutic plasma exchange. The study included nine females and one male with a diagnosis of classical TTP treated at multiple university hospital centers with protein A immunoabsorption (PAI) after having failed plasma exchange. The 10 patients had an age range 17–62 years. Prior to PAI, the patients had failed to respond to a mean of 15 (range 6–39) therapeutic plasma exchanges. Three patients had previous episodes of TTP.

Evaluation for response to PAI included serial measurements of serum creatinine, lactate dehydrogenase (LDH), hemoglobin, hematocrit, and platelet count before, during, and up to 18 months post-PAI treatment.

Seven of 10 study patients had resolution of their TTP. Six of the patients required six or fewer therapeutic PAIs and one required 12 treatments. All responding patients had evidence of improvement by the third PAI treatment. Three patients demonstrated no response to PAI, with two patients expiring from complications of TTP and one patient demonstrating a complete response to a subsequent therapy. No significant toxicity was noted with the use of PAI in this setting.

Protein A immunoabsorption in patients with classical TTP refractory to plasma exchange can produce durable complete remissions and warrants comparative studies. Am. J. Hematol. 55:55–58, 1997.

Key words: TTP; Protein A Immunoabsorbtion

INTRODUCTION

Treatment with plasma exchange results in remission in 80–90% of patients afflicted with classical thrombotic thrombocytopenic purpura (TTP). Subsequent management of patients with TTP who fail plasma exchange has no clearly defined options. The classical pentad of thrombocytopenia, microangiopathic hemolytic anemia, fever, and dysfunction of the renal and central nervous systems (CNS) defines the syndrome of TTP, but the pathophysiologic events leading to those symptoms remain obscure. A closely allied syndrome, hemolytic uremic syndrome (HUS), is characterized by thrombocytopenic microangiopathic hemolytic anemia and renal dysfunction but lacks fever and neurologic dysfunction. HUS is usually associated with gastroenteritis in children or with cancer chemotherapeutic agents [1–3]. In his benchmark article, Moschcowitz [4] postulated an etiology ''resulting from some powerful poison which had both agglutinative and

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hemolytic properties.'' Later investigators have suggested Moschcowitz's poison to be Calpain-a calcium-dependent proteinase, unusually large von Willebrand factor multimers, immune complexes, or autoantibodies to vascular endothelial cells [5–7]. The variable presentation, unpredictable clinical course, and clinical responsiveness to agents with obscure mechanisms of action suggest that the syndrome of TTP may represent an end product of a variety of provocative agents. During the 1970s and 1980s, plasma exchange and/or plasma infusions have become standard empiric therapy. Reported prospective trials suggest that plasma exchange using plasma volumes of $\geq$1–1.5 the patients' calculated plasma volume on a daily basis reduces mortality to 10–30% [8–11]. This compares favorably to historic reports of treatment with splenectomy, aspirin, vinca alkaloids, corticosteroids, and other forms of therapy in which mortality rates of 70–90% were reported [8–13]. To compound the difficulty of understanding TTP, the therapeutic effect of plasma therapy, i.e., removing or diluting a causative agent or alternatively providing a needed factor, is likewise speculative. The need for additive treatment with vinca alkaloids, corticosteroids, splenectomy, or antiplatelet agents remains unclear in initial treatment protocols [8,9,14]. The appropriate management of patients failing or only transiently responding to plasma therapy is likewise obscure. Dextran infusions, cryoprecipitate-depleted plasma exchanges, and high-dose intravenous γ-globulin have anecdotal reports of success, but the overall prognosis for plasma refractory patients is poor, and improvement in treatment approaches are clearly needed [12–19]. Another problem hindering development of effective forms of therapy for plasma refractory TTP stems from difficulty of prospectively identifying the small number of patients who will not benefit from plasma-based therapy.

Chemotherapy-induced hemolytic uremic syndrome (C-HUS) has clinical similarities to classical TTP. Both entities have consumptive thrombocytopenia, microangiopathic hemolytic anemia, and renal dysfunction as clinical manifestations [39]. Vascular endothelial damage secondary to chemotherapy agents or immune complexes is postulated as a potential causative factor in C-HUS. The failure of plasma exchange and the grim prognosis of patients with C-HUS parallel the usual clinical course of patients with TTP who fail to respond to plasma therapy. Recent reports have indicated that protein A immunoabsorption (PAI) reverses clinical manifestations and improves the long-term prognosis of patients with C-HUS whose malignancy was in remission [23,25,26]. Patients with C-HUS responding to PAI show significant drops in levels of circulating immune complexes [27]. Anecdotal case reports suggest a similar clinical improvement in plasma refractory TTP for patients treated with protein A immunoabsorption [27]. To clarify further the activity of PAI in plasma refractory TTP a retrospective multicenter chart review to identify patients treated with PAI was undertaken. The prior therapy, clinical and laboratory response to PAI, and long-term prognosis was evaluated.

MATERIALS AND METHODS

The charts of patients treated at six institutions (University of Florida, Jacksonville), University Hospital of Arkansas, Medical College of Georgia, New York Medical College, University of Minnesota, and the Coagulation Center of Summit Medical Center, Oakland, California, between January 1989 and April 1993 were retrospectively reviewed to identify patients with a diagnosis of TTP. All institutions were identified as frequent employers of PAI by the IMRE Corporation. All patients were required to have peripheral blood smear evidence of schistocytes, reticulocytosis, thrombocytopenia, normal coagulation parameters, and some evidence of renal and/or neurologic dysfunction. Patients were excluded for the following reasons: (1) history of treatment for active malignancy, (2) evidence of disseminated intravascular coagulation (DIC), (3) inadequate documentation of the diagnosis of TTP, (4) treatment with less than five consecutive daily plasma exchanges or employing exchange of less than one plasma volume per exchange prior to institution of PAI, and (5) failure to document response adequately. Complete response was defined as normalization of peripheral blood smear, platelet count, serum LDH, and neurologic function. Patients were allowed to have stable, asymptomatic laboratory evidence of renal dysfunction if all other criteria were fulfilled. Therapy in all patients consisted of on-line perfusion of 0.5–2.0 liters of plasma over a protein A immunosorbent Column (Prosorba). The total number of treatments for all patients was recorded. Serum LDH, platelet count, hemoglobin, hematocrit, and serum creatinine were measured at the start of PAI by standard techniques and followed serially in all patients. One patient (4) had no LDH recorded at the start of PAI but fulfilled all other criteria. The duration of response to PAI was calculated from normalization of laboratory and clinical parameters to time of last follow-up.

Patient Population

Baseline clinical and laboratory data obtained prior to institution of PAI are summarized in Tables I and II. Ten patients failing to exhibit any response in hematologic values and LDH to a minimum of five daily plasma exchanges during a current episode of TTP were identified. Three patients had previous episodes of active disease. Nine patients were female, one male with ages ranging from 17 to 62 years. Seven patients had received therapeutic modalities other than plasma exchange (PE),

TABLE I. Demographics

Patient No.	Age (yr)	Sex	Previous TTP	Other treatments
1	32	F	+	—
2	48	M	−	—
3	40	F	+	G/V/A
4	45	F	−	G
5	62	F	−	G
6	17	F	+	G/V/A
7	50	F	−	—
8	61	F	−	G
9	54	F	−	G/V/S/C
10	53	F	−	G/V/C

G, glucocorticoids; V, vinca alkaloids; A, antiplatelet agents; S, splenectomy; C, cryoprecipitate-depleted plasma.

TABLE II. Patient Characteristics

Patient No.	LDH	Plt	PE	PAI	R
1	3,650	7	5	6	R
2	3,600	10	8	5	F
3	413	11	16	6	R
4	N/A	40	8	6	R
5	772	44	16	4	F
6	1,585	32	8	5	R
7	540	67	16	12	R
8	1,296	55	11	5	R
9	2,587	21	27	6	F
10[a]	212	201	39	6	R

LD, serum lactate dehydrogenase (pre-PAI); Plt, platelet count (pre-PAI); PE, plasma exchange; PAI, protein A immunoabsorption; R, response; F, failure to respond to PAI; N/A, not available.

[a]Patient failed three attempts to taper frequency of plasma exchange. Values obtained during daily plasma exchange.

including vincristine, prednisone, splenectomy, antiplatelet agents, and PE with cryoprecipitate-depleted plasma (Table I). The number of plasma exchanges prior to PAI (not including previous episodes of TTP) ranged from 5 to 39, with 9 of 10 receiving 8 or more plasma exchanges. Five patients had exhibited no response or progressive disease after 5–11 plasma exchanges of at least one plasma volume. Five patients (1,3,4,5,7) had brief early improvement in LDH, platelet count, and symptoms with initiation of PE with FFP. All five subsequently had progressive deterioration with continued PE of identical or greater volume. Patient 10 had transient incomplete response to nine PE with FFP in 9 days. She then underwent PE with cryoprecipitate-depleted plasma, 30 times in 6 weeks. The patient maintained platelet counts and LDH within the normal range as long as daily treatments were continued. Attempts to decrease the frequency on three occasions resulted in dramatic worsening of LDH and platelet counts within 24–48 hr. All patients received at least four PAI treatments (range 4–12 mean = 6). No patient received other treatments while undergoing PAI therapy. All patients were evaluable for response and toxicity.

RESULTS

Complete resolution of symptoms occurred in seven out of ten patients. Three of the seven had persistent asymptomatic elevation of serum creatinine. Six of the seven responding patients had resolution of their TTP within six PAIs with one of the seven responders requiring 12 PAI treatments. The three nonresponding patients received four, five, and six PAI treatments. All three non-responding patients had continued worsening of clinical and laboratory parameters. Two of those patients expired secondary to hemorrhagic complications of TTP. The third patient had a complete response to subsequent dextran infusions and is currently without symptoms at 12 months. The seven responding patients are all alive without symptoms of TTP with follow-up ranging from 1 to 18 months (median 6 months). The patient who had failed 39 PEs was given PAI six times over 10 days with subsequent unmaintained normal LDH and platelet counts that have remained stable for 7 months. No major toxicities to PAI were noted in the treated patients. Transient nausea and headaches were common while the patient was undergoing treatment but resolved quickly post-treatment. No patients required cessation of PAI secondary to toxicity.

DISCUSSION

TTP now enjoys an excellent overall survival rate, with most large series reporting 80–90% survival of the initial episode of TTP when treated with daily high-volume plasma exchange. The unfortunate 10–20% of patients who fail plasma therapy, on the other hand, have an unfavorable outcome. In the past, treatment forms included splenectomy, vincristine, cryoprecipitate-depleted plasma infusions/exchanges, high-dose intravenous immunoglobulin, and antiplatelet agents. Splenectomy as a treatment has case reports of success, but a recent report found six out of nine patients refractory to plasma exchange to be refractory to splenectomy as well [20]. Vincristine either alone or combined with plasma therapy has likewise produced variable results. High-dose intravenous infusions of γ-globulins have, in several case reports, produced responses, but no large series of patients or long-term follow-up exists [16–18]. Exchange with cryoprecipitate-depleted plasma as reported by Byrnes and Moake and colleagues [24] has produced responses, but again its role is undefined.

The rationale for PAI in plasma refractory TTP stemmed from reported success in a clinically similar entity, chemotherapy-induced hemolytic uremic syndrome (C-HUS) [23,25,26]. In this retrospective study, application of PAI to 10 patients with plasma refractory or plasma exchange dependant TTP resulted in seven responses. All patients exhibited improvement in LDH

and platelet count within 7 days after institution of PAI. Two patients required five, and four patients six PAI treatments for stable remission. No patient received maintenance PAI. Toxicity was minimal, confined to flu-like symptoms. No relapses post-PAI were noted, although follow-up was of short duration in most patients.

This report provides useful information but also raises important questions. What defines response in treatment of TTP? In a report of the Canadian Apheresis Group, Rock et al. [9] judged two consecutive days of >150,000 platelet count with no deterioration in neurologic status as a ''complete'' response. Many patients with this definition of complete response will relapse or as our patient 10, be PE dependent. Another dilemma arises in the patient whose course continually worsens despite adequate PE. Unfortunately, no criteria currently exist to prospectively identify these patients (10–20%) who will be refractory to plasma-based therapy. In this group of 10 patients, the criteria of worsening life-threatening neurologic, renal, or hematologic symptoms after 5–11 daily, greater than one plasma volume, plasma exchanges or failure to maintain response after a prohibitive number (16–39) of exchanges was used. The question of FFP or cryoprecipitate-depleted plasma as the optimum exchange vehicle was not addressed in our retrospective series.

Until the above questions are answered, difficulties in deciding when an individual patient in ''refractory'' to PE will remain.

These questions aside, this retrospective case review demonstrates PAI to have activity in TTP patients fitting defined criteria as being refractory to plasma exchange. This activity of PAI requires better definition in a prospective trial.

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